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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Pyrazinoindoles

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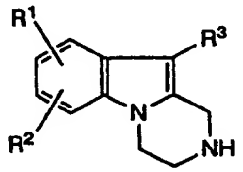
Notice: This application is as filed and may therefore contain an incomplete specification.

Canada

Abstract

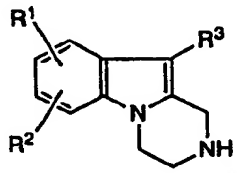
The novel pyrazinoindoles of the general formula



I

wherein R^1 signifies hydrogen, halogen, trifluoromethyl, lower alkyl, hydroxy or lower alkoxy, R^2 signifies hydrogen or halogen and R^3 signifies hydrogen, lower alkoxy or lower alkylthio, with the proviso that R^3 can only signify hydrogen when R^1 and R^2 are both different from hydrogen, and pharmaceutically acceptable acid addition salts of the compounds of formula I are suitable for the treatment or prophylaxis of central nervous disorders such as depression, bipolar disorders, anxiety, sleep and sexual disorders, psychosis, schizophrenia, migraine and other conditions associated with cephalic pain or other pain types, personality disorders and obsessive-compulsive disorders, social phobia or panic disorders, mental organic disorders, mental disorders in childhood, aggressiveness, age-associated memory impairement and behavioral symptoms, addiction, obesity, bulimia etc.; neural damage resulting from trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of gastrointestinal tract motility.

The present invention is concerned with pyrazinoindoles. In particular, it is concerned with compounds of the general formula



I

wherein R^1 signifies hydrogen, halogen, trifluoromethyl, lower alkyl, hydroxy or lower alkoxy, R^2 signifies hydrogen or halogen and R^3 signifies hydrogen, lower alkoxy or lower alkylthio, with the proviso that R^3 can only signify hydrogen when R^1 and R^2 are both different from hydrogen, and pharmaceutically acceptable acid addition salts of the compounds of formula I.

These compounds and salts are novel and are distinguished by valuable therapeutic properties. In particular, they are suitable for the treatment or prophylaxis of central nervous disorders such as depression, bipolar disorders, anxiety, sleep and sexual disorders, psychosis, schizophrenia, migraine and other conditions associated with cephalic pain or other pain types, personality disorders and obsessive-compulsive disorders, social phobia or panic disorders, mental organic disorders, mental disorders in childhood, aggressiveness, age-associated memory impairement and behavioral symptoms, addiction, obesity, bulimia etc.; neural damage resulting from trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of gastrointestinal tract motility.

Objects of the present invention are the compounds of general formula I and their pharmaceutically acceptable acid addition salts per se and as pharmaceutically active substances, medicaments containing a compound of general formula I or a

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pharmaceutically acceptable acid addition salt thereof, the manufacture of such medicaments, the use of compounds of general formula I and their pharmaceutically acceptable acid addition salts in the treatment or prophylaxis of diseases and disorders of the kind referred to earlier or for the manufacture of medicaments for the treatment of said illnesses and disorders, as well as the manufacture of the compounds of formula I above and their pharmaceutically acceptable acid addition salts and intermediates suitable therefor.

The term "lower" denotes residues and compounds with a maximum of seven, preferably a maximum of four, carbon atoms. The term "alkyl" denotes straight-chain or branched, saturated hydrocarbon residues such as methyl, ethyl, isopropyl or t-butyl. The term "alkoxy" denotes alkyl groups bonded via an oxygen atom, such as methoxy, ethoxy, propoxy, isopropoxy or butoxy. The term "alkylthio" denotes alkyl groups bonded via a sulphur atom, such as methylthio or ethylthio. The term "halogen" denotes the four forms F, Cl, Br and I.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like. Such salts can be manufactured readily by any person skilled in the art having regard to the state of the art and taking into consideration the nature of the compound to be converted into a salt.

Preferred compounds of formula I are those in which R^3 signifies lower alkoxy, especially those in which R^1 singifies hydrogen or halogen and R^2 signifies halogen.

Further preferred compounds are those in which R^3 signifies hydrogen and R^1 and R^2 each signify halogen.

Quite especially preferred compounds are:

9-Chloro-8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole;

8-fluoro-10-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]-indole;

9-fluoro-10-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]-indole;

9-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole; and

9-chloro-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole.

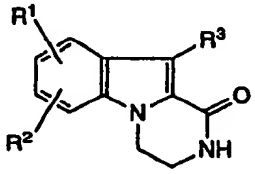
Further examples of compounds of formula I are:

8-Chloro-10-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]-indole;

7-chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole; and

8-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole.

The compound of formula I and their pharmaceutically usable acid addition salts can be manufactured in accordance with the invention by reducing a compound of the general formula



II

wherein R^1, R^2 and R^3 have the above significance, and, if desired, converting a compound of formula I obtained into a pharmaceutically acceptable acid addition salt.

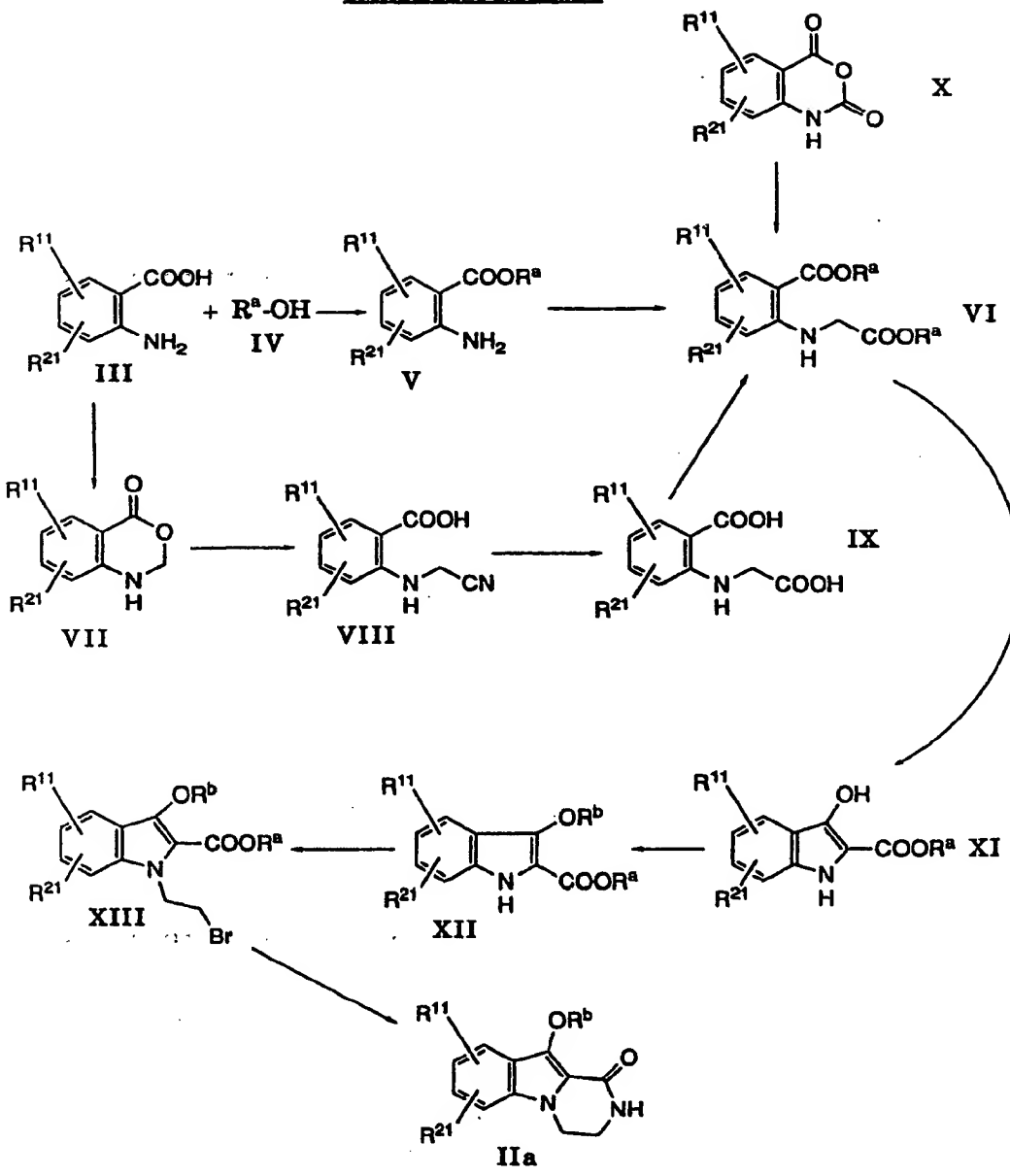
The reduction is preferably carried out by treatment with lithium aluminium hydride or similar reducing agents such as diborane and the like. The reaction is effected in an inert solvent, such as e.g. tetrahydrofuran, in a temperature range of room

temperature to the boiling temperature, preferably at the boiling temperature.

As pharmaceutically acceptable acid addition salts of the compounds of formula I there come into consideration not only salts with inorganic acids, but also salts with organic acids. Examples of such salts are hydrochlorides, hydrobromides, nitrates, sulphates, phosphates, citrates, formates, fumarates, maleates, acetates, succinates, tartrates, methanesulphonates, p-toluenesulphonates and the like. These salts can be manufactured according to methods which are known per se and which are familiar to any person skilled in the art.

The various compounds which are used as starting materials can be prepared, for example, in accordance with the following Reaction Schemes and the descriptions of the various reactions which follow each of them.

Reaction Scheme I



R^{11} signifies hydrogen, halogen, trifluoromethyl, lower alkyl, hydroxy or lower alkoxy, R^{21} signifies hydrogen or halogen and R^a and R^b each signify lower alkyl.

By reacting an anthranilic acid of formula III with an alcohol of formula IV there is obtained a corresponding ester of formula V. The esters of formula V are accessible from compounds of formulae III and IV according to conventional methods, see, for example, Tetrahedron 33, 217 (1977), or can be prepared in an analogous manner.

A compound of formula VI is obtained by treating an ester of formula V with an alkyl α-halocarboxylate such as, for example, ethyl α-bromoacetate. Conveniently, the alkyl α-halocarboxylate simultaneously serves as the reagent and as the solvent, with a carbonate, for example potassium carbonate, being added in equimolar amount. This reaction is preferably carried out in a temperature range of about 20°C to about 80°C analogously to a process described in Pr. roy. Soc. 148 (1958).

The compounds of formula VI can, however, also be prepared by firstly converting an anthranilic acid of formula III with formaldehyde into a compound of formula VII, with this reaction conveniently being carried out in a solvent which is inert under the reaction conditions, such as, for example, lower alcohols, preferably methanol. Subsequently, the thus-obtained compound of formula VII is converted into a compound of formula VIII with a cyanide such as, for example, potassium cyanide in a polar solvent, preferably water, and at a reaction temperature of about 60°C. Compounds of formula IX are obtained by treating a compound of formula VIII with aqueous alkali, for example sodium hydroxide solution. This reaction is preferably effected in a temperature range of about 100°C to about 120°C. The compounds of formula IX can then be converted into the compounds of formula VI with alcohols according to methods which are known per se and which are familiar to any person skilled in the art.

The compounds of formula VI can, however, also be prepared by reacting an isatoic anhydride of formula X with an ethyl α-haloacetate, such as, for example, ethyl bromoacetate in a polar solvent such as DMSO and subsequently reacting with an alcohol.

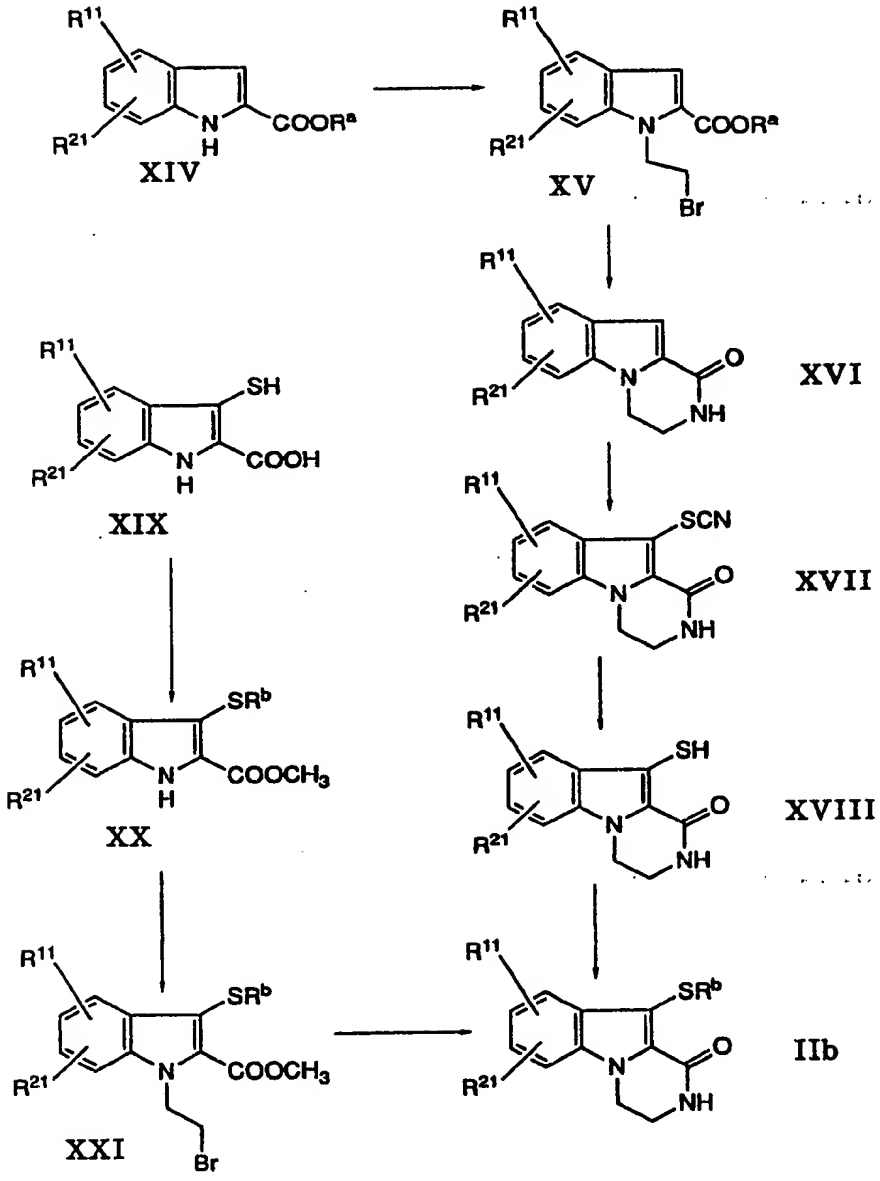
By cyclizing a compound of formula VI there is obtained an indole of formula XI. These compounds are known, see, for example, J. Heterocyclic Chem. 16, 221 (1979), or can be prepared in an analogous manner.

Compounds of formula XII are obtained by reacting an indole of formula XI with an alkylating agent, for example, with a dialkyl sulphate or with diazomethane. This reaction is effected in alcoholic solvents, preferably methanol, at room temperature.

A compound of formula XIII is obtained by treating a compound of formula XII with 1,2-dibromoethane. This reaction is carried out under phase transfer catalysis conditions: the reaction is effected while stirring in a two-phase system comprising water and a water-immiscible organic solvent in the presence of a strong base and a phase transfer catalyst. Conveniently, 1,2-dibromoethane, which simultaneously serves as the reagent, can be used as the organic solvent. Potassium hydroxide or sodium hydroxide is suitable, for example, as the strong base. The usual phase transfer catalysts can be used. Suitable catalysts are, for example, benzyltrimethylammonium chloride, tetrabutylammonium bromide and similar compounds. The reaction is preferably carried out in a temperature range of about 20°C to about 80°C.

By cyclizing a compound of formula XIII with ammonia there is obtained a compound of formula IIa, i.e. a compound of formula II in which R^3 signifies lower alkoxy. The reaction is carried out in an autoclave at reaction temperatures of 80-100°C, preferably at 80°C.

Reaction Scheme II



R^{11}, R^{21}, R^a and R^b have the significances given above.

A compound of formula XV is obtained by treating an indole of formula XIV with 1,2-dibromoethane. This reaction is effected under the phase transfer catalysis conditions described above, namely in connection with the preparation of the compounds of formula XIII from the compounds of formula XII.

The compounds of formula XIV are known, see, for example, Synthesis 1985, 186, or can be prepared in an analogous manner.

A compound of formula XVI is obtained by cyclizing a compound of formula XV with ammonia. The reaction is carried out in an autoclave at reaction temperatures of 50 to 100°C, preferably at 80°C.

Where R^{11} and R^{21} in formula XVI are different from hydrogen, then this is a compound of formula II in which R^3 signifies hydrogen (whereby according to definition R^1 and R^2 must both be different from hydrogen), and by reduction there can be manufactured therefrom in accordance with the invention a corresponding compound of formula I.

A compound of formula XVII is obtained by reacting a compound of formula XVI with an alkali thiocyanate, for example potassium thiocyanate, and bromine in an alcohol such as, for example, methanol. This reaction is effected in a temperature range of -70°C to room temperature analogously to the method described in J. Am. Chem. Soc. 82, 2742 (1960).

A compound of formula XVIII is obtained by treating a compound of formula XVII with a base, for example sodium hydroxide, in a pH range of 10 to 14 and a temperature range of 80°C to 100°C. This reaction is effected in polar solvents, preferably water/alcohol mixtures.

A compound of formula IIb, i.e. a compound of formula II in which R^3 signifies lower alkylthio, is obtained by reacting a

compound of formula XVIII with an alkylating agent, for example, with a dialkyl sulphate or with diazomethane.

The compounds of formula IIb can, however, also be prepared from 3-mercapto-2-indolecarboxylic acids of formula XIX. A compound of formula XX is obtained by reacting a compound of formula XIX with an alkylating agent, for example, with a dialkyl sulphate or with diazomethane. The compounds of formula XX are known, see, for example, J. Am. Chem. Soc. 82, 2742 (1960), or can be prepared in an analogous manner.

A compound of formula XXI is obtained by treating compounds of formula XX with 1,2-dibromoethane. This reaction is effected analogously to the phase transfer catalysis conditions described above, namely in connection with the preparation of the compounds of formula XIII from the compounds of formula XII.

A compound of formula IIb, i.e. a compound of formula II in which R^3 signifies lower alkylthio, is obtained by cyclizing a compound of formula XXI with ammonia.

The compounds of formula II which are used as intermediates are novel and are also an object of the present invention. The remaining compounds which are used as starting materials or intermediates belong to classes of substances which are known per se.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable acid addition salts posses valuable pharmacodynamic properties. They have the capacity to bind to serotinin receptors and are accordingly suitable for the treatment or prophylaxis of illnesses and disorders of the kind referred to earlier and, respectively, for the manufacture of corresponding medicaments.

The binding of compounds of formula I in accordance with the invention to serotonin receptors was determined in vitro by

standard methods. The preparations were investigated in accordance with the tests given hereinafter:

a) for the binding to the $5HT_{1A}$ receptor in accordance with the 3H-8-OH-DPAT binding assay according to the method of J.S. Peroutka, Biol. Psychiatry 20, 971-979 (1985).

b) For the binding to the $5HT_{1B}$ receptor in accordance with the binding assay according to the method of S.J. Peroutka, Brain Research 344, 167-171 (1985) or M.B. Emerit et al., Biochem. Pharmacol. 34, 883-892 (1985).

c) For the binding to the $5HT_{1C}$ receptor in accordance with the 3H-mesulergine binding assay according to the method of A.Pazos et al., Europ. J. Pharmacol. 106, 539-546 or D.Hayer, Receptor Research 8, 59-81 (1988).

d) For the binding to the $5HT_2$ receptor in accordance with the 3H-metanserine binding assay according to the method of J.E.Leysen, Molecular Pharmacology 21, 301-304 (1981).

The IC_{50} values of the test substances were determined, i.e. that concentration in nMol by which 50% of the ligands bound to the receptors are displaced.

The thus-determined activities of some compounds in accordance with the invention as well as those of some comparative compounds will be evident from the following Table:

Test methods

Substance	a	b	c	d
Buspirone	19.50		3700.0	990.0
NAN-190	0.56		1800.0	581.0
5HT	1.50	4.33	9.5	1730.0

Metergoline	4.80		5.5	64.9
mCPP	227.00	74.20	53.0	319.0
RU 24969	8.00	1.84	159.0	2500.0
CP 93129	1620.00	19.70	2780.0	29200.0
Ritanserine	5750.00		37.0	3.1
Pirenperone	2870.00		37.0	2.9
A	687.00		775.0	12500.0
B	2370.00	398.00	367.0	9390.0
C	1070.00	327.00	221.0	5170.0
D	657.00	199.00	195.0	3140.0
E	407.00	56.10	83.8	1020.0
F	425.00	370.00	406.0	9460.0
G	298.00		269.0	2810.0
H	354.00		90.5	1030.0
I	106.00		219.0	2270.0
J	512.00		66.0	374.0
K	705.00		1350.0	11200.0
L	459		251	5850
M	690		923	3030
N	964		57	902

A = 10-Methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]indole

B = 8-Fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole

C = 9-Fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole

D = 8-Chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole

E = 9-Bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole

F = 7-Chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole

G = 8-Bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole

H = 9-Chloro-8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole

I = 1,2,3,4-Tetrahydro-10-methoxy-9-methyl-pyrazino-[1,2-a]indole

J = 9-Trifluoromethyl-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole

K = 1,2,3,4-Tetrahydro-10-methylthiopyrazino[1,2-a]-indole

L = 7,9-Dichloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole

M = 6-Bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole

N = 9-Chloro-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole.

Some of the compounds of formula I were also tested in animal tests.

Antagonism of mCPP-induced penile erections (rat)

It has been shown that penile erections depend on the stimulation of $5HT_{1c}$ receptors, see Berendsen & Broekkamp, Eur. J. Pharmacol. 135, 179-184 (1987). The test substance is administered to animals pre-treated with mCCP and the number of penile erections occurring within 45 minutes is determined.

The ID_{50} is that dosage of test substance which inhibits the number of these erections by 50%.

Substance	ID_{50} (mg/kg, s.c.)
B	4.2
C	17.0
E	4.3
I	2.7
N	4.2

Antagonism of quipazine-induced head shakes (rat)

"Head shakes" depend on the stimulation of $5HT_2$ receptors, see Goodwin & Green, Br. J. Pharmacol. 84, 743-753 (1985). The test substance is administered to animals pre-treated with quipazine and the number of "head shakes" occurring within 45 minutes is determined. The ID_{50} is that dosage of test substance which inhibits the number of these "head shakes" by 50%.

Substance	ID_{50} (mg/kg, s.c.)
E	3.1
I	3.0
N	5.2

In performing the animal tests described above the test substances B, C, E, I and N were administered to the animals (rats) in doses up to 30 mg/kg s.c. without any toxic effects being observed. From this it can be concluded that doses having a toxic effect must be higher than the mentioned doses of 30 mg/kg s.c.

The compounds of formula I and the pharmaceutically acceptable acid addition salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets,

dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions, or nasally.

The compounds of formula I and the pharmaceutically acceptable acid addition salts of the compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the manufacture of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose and the like. Suitable carriers for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable acid addition salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their manufacture, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical administration form, together with one or more therapeutic inert carriers.

In accordance with the invention compounds of general formula I as well as their pharmaceutically acceptable acid addition salts can be used in the treatment or prophylaxis of central nervous disorders such as depression, bipolar disorders, anxiety, sleep and sexual disorders, psychosis, schizophrenia, migraine and other conditions associated with cephalic pain or other pain types, personality disorders and obsessive-compulsive disorders, social phobia or panic disorders, mental organic disorders, mental disorders in childhood, aggressiveness, age-associated memory impairement and behavioral symptoms, addiction, obesity, bulimia etc.; neural damage resulting from trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of gastrointestinal tract motility and, respectively, for the manufacture of corresponding medicaments. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In the case of oral administration the daily dosage lies in a range of about 0.1 mg per dosage to about 500 mg per day of a compound of general formula I or the corresponding amount of a pharmaceutically acceptable acid addition salt thereof, although the upper limit can also be exceeded when this is shown to be indicated.

The following Examples illustrate the present invention in more detail. However, they are not intended to limit its scope in any manner. All temperatures are given in degrees Celsius.

Example 1

a) A suspension of 1.7 g (7.7 mmol) of ethyl 3-methoxy-indole-2-carboxylate in 30 ml of dibromoethane was treated with 30 ml of 28% NaOH and 200 mg (0.6 mmol) of tetrabutyl-ammonium bromide. The mixture was stirred at 50° for 1.5 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent

was distilled off and the solid residue was suspended in 70 ml of liquid ammonia and stirred in an autoclave at 80° for 24 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. There were obtained 1.6 g (96%) of crude 10-methoxy-1,2,3,4-tetrahydro-pyrazino[1,2-a]indol-1-one which was used in the next step without purification.

b) A solution of 0.65 g (3 mmol) of 10-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-one in 25 ml of dry THF was treated with 228 mg (6 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water and 30 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 20 ml of ethanol, treated with 10 ml of saturated ethanolic HCl solution and the separated crystals were filtered off under suction at 0°. There was obtained 0.48 g (67%) of 10-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 208° (dec.).

Example 2

a) A suspension of 15.2 g (83 mmol) of ethyl 5-fluoro-anthranilate and 8.8 g (83 mmol) of sodium carbonate in 46 ml (415 mmol) of methyl bromoacetate was stirred at 80° for 18 hours. The mixture was evaporated in a vacuum and the residue was treated with 184 ml of water, 18.4 ml of ethanol and 18.4 ml of a 25% ammonia solution. The mixture was stirred at room temperature for 2 hours. The resulting precipitate of N-[4-fluoro-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester was triturated with hexane, filtered off under suction and dried. There were obtained 12.5 g (59%) of N-[2-(ethoxycarbonyl)-4-fluoro-phenyl]-glycine ethyl ester as pale yellow crystals with m.p. 66-67°.

b) A solution of 4.9 g (214 mmol) of sodium in 70 ml of ethanol was treated with a solution of 27.3 g (102 mmol) of N-[2-(ethoxycarbonyl)-4-fluoro-phenyl]-glycine ethyl ester in

200 ml of ether. The mixture was boiled under reflux for 2 hours and, after cooling, treated with water and extracted with ether. The aqueous phase was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction, rinsed with a small amount of water and dried in a drying oven. 15.3 g (67%) of crude ethyl 5-fluoro-3-hydroxyindole-2-carboxylate were obtained. A sample was recrystallized from toluene and then showed a m.p. of 152-154°.

c) A suspension of 10 g (44 mmol) of ethyl 5-fluoro-3-hydroxyindole-2-carboxylate in 400 ml of methanol was treated with 150 ml of a 60% ethereal diazomethane solution. 50 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off and there were obtained 11.8 g (99%) of amorphous ethyl 1-(2-bromoethyl)-5-fluoro-3-methoxyindole-2-carboxylate.

MS: m/e (% basic peak): 343, 345 (M^+,58), 328, 330 (14), 264 (34), 250 (46), 218 (83), 41 (100).

e) A suspension of 11.8 g (34.3 mmol) of ethyl 1-(2-bromoethyl)-5-fluoro-3-methoxyindole-2-carboxylate in 330 ml of liquid ammonia was stirred in an autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. After recrystallization from ethyl acetate there were obtained 4.5 g (57%) of 8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as white crystals with m.p. 220-223°.

f) A solution of 1.5 g (6.4 mmol) of 8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 30 ml of dry THF was treated with 500 mg (13 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water, the mixture was diluted with 100 ml of ether and 50 g of sodium sulphate were added thereto. After filtration and concentration of the filtrate the residue was dissolved in 50 ml of ethanol, treated with 20 ml

of saturated ethanolic HCl solution and stirred at room temperature for half an hour, whereby crystals separated. There were obtained 1.2 g (73%) of 8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 219-221°.

Example 3

a) A suspension of 112 g (65 mmol) of methyl 6-fluoro-anthranilate and 6.9 g (65 mmol) of sodium carbonate in 36 ml (325 mmol) of methyl bromoacetate was stirred at 80° for 18 hours. The mixture was evaporated in a vacuum and the residue was treated with 180 ml of water, 18 ml of ethanol and 18 ml of a 25% ammonia solution. The mixture was stirred at room temperature for 2 hours. There were obtained 14.6 g (91.2%) of a precipitate of N-[3-fluoro-2-(methoxycarbonyl)-phenyl]-glycine methyl ester which was used in the next step without further purification.

b) A solution of 2.7 g (117 mmol) of sodium in 40 ml of methanol was treated with a solution of 13.5 g (56 mmol) of N-[3-fluoro-2-(methoxycarbonyl)-phenyl]-glycine methyl ester in 110 ml of ether. The mixture was boiled under reflux for 2 hours and, after cooling, treated with water and extracted with ether. The aqueous phase was adjusted to pH 8 with dry ice, the separated crystals were filtered off under suction and rinsed with a small amount of water. The residue was suspended in 400 ml of methanol and treated with 150 ml of a 60% ethereal diazomethane solution. 50 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off. The residue was triturated with a mixture of 60 ml of n-hexane and 60 ml of ether and the crystals were filtered off under suction. There were obtained 7.6 g (61%) of methyl 4-fluoro-3-methoxy-indole-2-carboxylate as white crystals with m.p. 137-139°.

c) A suspension of 7.6 g (34 mmol) of methyl 4-fluoro-3-methoxy-indole-2-carboxylate in 170 ml of dibromoethane was treated with 85 ml of 28% NaOH and 564 mg (1.75 mmol) of tetrabutylammonium bromide. The mixture was stirred at 50° for 1.5 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 340 ml of liquid ammonia and stirred in an autoclave at 80° for 24 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. After recrystallization from alcohol there were obtained 4.1 g (51%) of 9-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as white crystals with m.p. 190-193°.

d) A solution of 1.5 g (6.4 mmol) of 9-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 30 ml of dry THF was treated with 500 mg (13 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water, the mixture was diluted with 100 ml of ether and 50 g of sodium sulphate were added thereto. After filtration and concentration of the filtrate the residue was dissolved in 50 ml of ethanol, treated with 20 ml of saturated ethanolic HCl solution and stirred at 0° for one hour, whereby crystals separated. There were obtained 1.3 g (79%) of 9-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 227-231°.

Example 4

a) A suspension of 12 g (64.6 mmol) of methyl 5-chloro-anthranilate and 6.9 g (65 mmol) of sodium carbonate in 36 ml (323 mmol) of ethyl bromoacetate was stirred at 80° for 18 hours. The mixture was evaporated in a vacuum and the residue was treated with 180 ml of water, 18 ml of ethanol and 18 ml of a 25% ammonia solution. The mixture was stirred at room temperature for 2 hours. The resulting precipitate was recrystallized from ethanol/water and there were obtained 11.2 g

(64%) of N-[4-chloro-2-(methoxycarbonyl)-phenyl]-glycine ethyl ester as white needles with m.p. 82-83°.

b) A solution of 1.25 g (54.4 mmol) of sodium in 20 ml of ethanol was treated with a solution of 6.87 g (25.3 mmol) of N-[4-chloro-2-(methoxycarbonyl)-phenyl]-glycine ethyl in 20 ml of ether. The mixture was boiled under reflux for 2 hours and, after cooling, treated with water and extracted with ether. The aqueous phase was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction, rinsed with a small amount of water and dried in a drying oven. 4.8 g (79%) of crude ethyl 5-chloro-3-hydroxyindole-2-carboxylate were obtained. A sample was recrystallized from toluene and then showed a m.p. of 172-174°.

c) A suspension of 2.6 g (10.8 mmol) of ethyl 5-chloro-3-hydroxyindole-2-carboxylate in 100 ml of methanol was treated with 100 ml of a 60% ethereal diazomethane solution. 50 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off and there were obtained 2.7 g (quant.) of crude pulverous ethyl 5-chloro-3-methoxyindole-2-carboxylate. A small sample was recrystallized from ethyl acetate/hexane and showed a m.p. of 125-127°.

d) A solution of 1.5 g (5.9 mmol) of ethyl 5-chloro-3-hydroxy-indole-2-carboxylate in 30 ml of dibromoethane was treated with 30 ml of 28% NaOH and 100 mg (0.3 mmol) of tetrabutyl-ammonium bromide. The mixture was stirred at 50° for 1 hour. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 80 ml of liquid ammonia and stirred in an autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. After recrystallization from ethyl acetate there was obtained 0.8 g (54.4%) of 8-chloro-

1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as white crystals with m.p. 218-220°.

e) A solution of 0.6 g (2.4 mmol) of 8-chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 25 ml of dry THF was treated with 200 mg (5.2 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water, the mixture was diluted with 100 ml of ether and 30 g of sodium sulphate were added thereto. After filtration and concentration of the filtrate the residue was dissolved in 10 ml of ethanol, treated with 5 ml of saturated ethanolic HCl solution and stirred at room temperature for half an hour, whereby crystals separated. There was obtained 0.48 g (73%) of 8-chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as yellowish crystals with m.p. 234-235°.

Example 5

a) A suspension of 15.5 g (63.5 mmol) of ethyl 6-bromo-anthranilate and 6.7 g (63.5 mmol) of sodium carbonate in 35 ml (318 mmol) of ethyl bromoacetate was stirred at 80° for 18 hours. The mixture was evaporated in a vacuum and the residue was treated with 180 ml of water, 18 ml of ethanol and 18 ml of a 25% ammonia solution. The mixture was stirred at room temperature for 2 hours. The emulsion was extracted with 350 ml of ether and the organic phase was washed three times with 175 ml of water each time and with 35 ml of saturated sodium chloride solution. After drying and distillation there were obtained 20.3 g (96.8%) of N-[3-bromo-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester as an orange oil which was used in the next step without further purification.

b) A solution of 1.6 g (69 mmol) of sodium in 60 ml of ethanol was treated with a solution of 19 g (57.5 mmol) of N-[3-bromo-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester in 60 ml of ether. The mixture was stirred at room temperature for 2 hours, the yellow suspension was diluted with 580 ml of water and adjusted

to pH 8 with dry ice. The separated crystals were filtered off under suction, washed with a small amount of water and dried at 30° in a vacuum. There were obtained 14.7 g (90%) of ethyl 4-bromo-3-hydroxyindole-2-carboxylate as beige crystals with m.p. 155-160°.

c) A suspension of 8.5 g (30 mmol) of ethyl 4-bromo-3-hydroxyindole-2-carboxylate in 300 ml of methanol was treated with 150 ml of a 60% ethereal diazomethane solution. 50 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off and the residue was triturated in 60 ml of n-hexane. There were obtained 7 g (79%) of ethyl 4-bromo-3-methoxyindole-2-carboxylate as white crystals with m.p. of 137-139°.

d) A solution of 7 g (23.5 mmol) of ethyl 4-bromo-3-methoxyindole-2-carboxylate in 117 ml of dibromoethane was treated with 59 ml of 28% NaOH and 380 mg (1.17 mmol) of tetrabutylammonium bromide. The mixture was stirred at room temperature for 6 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off, the residue was suspended in 230 ml of liquid ammonia and stirred in an autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. There were obtained 6.37 g (92%) of crude 9-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one. A sample was recrystallized from ethanol and then showed a m.p. of 205-206°.

e) A solution of 4.04 g (13.7 mmol) of 9-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 130 ml of dry THF was treated with 1 g (27 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water and 13 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 55 ml of

ethanol, treated with 30 ml of saturated ethanolic HCl solution. The crystals were filtered off under suction and recrystallized from methanol. There were obtained 1.56 g (36%) of 9-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 236-238° (dec.).

Example 6

a) A suspension of 10 g (50 mmol) of ethyl 4-chloroanthranilate and 5.3 g (50 mmol) of sodium carbonate in 20 ml (180 mmol) of ethyl bromoacetate was stirred at 80° for 18 hours. After cooling the mixture was treated with 20 ml of ethanol and 20 ml of a 25% ammonia solution. There were obtained 10 g (70%) of a precipitate of N-[4-chloro-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester which was used in the next step without purification.

b) A solution of 2.03 g (88.2 mmol) of sodium in 30 ml of ethanol was treated with a solution of 12 g (42 mmol) of N-[4-chloro-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester in 150 ml of ether. The mixture was boiled under reflux for 2 hours and, after cooling, treated with water and extracted with ether. The aqueous phase was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction. They were rinsed with a small amount of water and dried at 50° in a vacuum. There were obtained 6.15 g (61%) of ethyl 6-chloro-3-hydroxyindole-2-carboxylate with m.p. 167-170°.

c) A suspension of 3 g (12.5 mmol) of ethyl 6-chloro-3-hydroxyindole-2-carboxylate in 125 ml of methanol was treated with 100 ml of a 60% ethereal diazomethane solution. 50 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off and there were obtained 3.27 g (94.5%) of ethyl 6-chloro-3-methoxyindole-2-carboxylate which was used in the next step without further purification.

d) A solution of 3.27 g (12.5 mmol) of ethyl 6-chloro-3-methoxyindole-2-carboxylate in 60 ml of dibromoethane was treated with 60 ml of 28% NaOH and 200 mg (0.6 mmol) of tetrabutylammonium bromide. The mixture was stirred at 50° for 2 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 80 ml of liquid ammonia and stirred in an autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. After recrystallization from ethanol there were obtained 2.4 g (74.3%) of 7-chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as white crystals with m.p. 218-220°.

e) A solution of 0.95 g (3.7 mmol) of 7-chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 40 ml of dry THF was treated with 0.28 g (7.5 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water and 30 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 20 ml of ethanol and treated with 10 ml of saturated ethanolic HCl solution. The crystals were filtered off under suction and recrystallized from ethanol. There was obtained 0.35 g (34%) of 7-chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 228-230°.

Example 7

a) A suspension of 13 g (53 mmol) of ethyl 5-bromo-anthranilate and 5.7 g (53 mmol) of sodium carbonate in 30 ml (270 mmol) of ethyl bromoacetate was stirred at 80° for 40 hours. The mixture was evaporated in a vacuum and the residue was treated with 145 ml of water, 14.5 ml of ethanol and 14.5 ml of a 25% ammonia solution. The mixture was stirred at room temperature for 2 hours. The separated crystals were washed with hexane and dried at 45° in a vacuum. There were

obtained 13.08 g (74.4%) of N-[4-bromo-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester with a m.p. of 95-96°.

b) A solution of 1 g (43.5 mmol) of sodium in 50 ml of ethanol was treated with a suspension of 13 g (39.3 mmol) of N-[4-bromo-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester in 25 ml of ether and in 25 ml of ethanol. The mixture was boiled under reflux for 2 hours, and, after cooling, treated with water. The mixture was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction. There were obtained 8.3 g (74%) of crude ethyl 5-bromo-3-hydroxyindole-2-carboxylate which was used in the next step without further purification.

c) A suspension of 8.2 g (29 mmol) of ethyl 5-bromo-3-hydroxyindole-2-carboxylate in 300 ml of methanol was treated with 150 ml of a 60% ethereal diazomethane solution. 100 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off and there were obtained 8.4 g (quant.) of crude pulverous ethyl 5-bromo-3-methoxyindole-2-carboxylate. A small sample was recrystallized from ethanol and showed a m.p. of 136-138°.

d) A solution of 8.4 g (28.2 mmol) of ethyl 5-bromo-3-methoxyindole-2-carboxylate in 130 ml of dibromoethane was treated with 130 ml of 28% NaOH and 440 mg (1.3 mmol) of tetrabutylammonium bromide. The mixture was stirred at room temperature for 4 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 280 ml of liquid ammonia and stirred in an autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. There were obtained 6.3 g (75.7%) of 8-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as beige crystals with m.p. 209-211°.

e) A solution of 0.9 g (3 mmol) of 8-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 60 ml of dry THF was treated with 20 ml of a 1N diborane solution in THF and boiled under reflux for two hours. The excess hydride was decomposed using 5 ml of saturated ethanolic HCl and the mixture was heated under reflux for one hour. The mixture was made basic with concentrated sodium hydroxide solution and extracted with ethyl acetate and water. The organic phase was dried with sodium sulphate and the solvent was removed. The residue was dissolved in 10 ml of ethanol and filtered off. By the addition of 10 ml of saturated ethanolic HCl solution there was obtained 0.5 g (51.6%) of 8-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as pale yellow crystals with m.p. 239°.

Example 8

a) A suspension of 3 g (14 mmol) of ethyl 6-chloro-5-fluoro-anthranilate and 1.5 g (14 mmol) of sodium carbonate in 8 ml (71 mmol) of ethyl bromoacetate was stirred at 80° for 30 hours. The mixture was evaporated in a vacuum and the residue was treated with 33 ml of water, 3.3 ml of ethanol and 3.3 ml of a 25% ammonia solution. The mixture was extracted with ethyl acetate and the organic phase was dried with sodium sulphate. The solvent was distilled off and there were obtained 4 g (95%) of N-[3-chloro-2-(ethoxycarbonyl)-4-fluoro-phenyl]-glycine ethyl ester as an orange oil which was used in the next step without further purification.

b) A solution of 0.33 g (14.3 mmol) of sodium in 15 ml of ethanol was treated with a suspension of 3.6 g (11.8 mmol) of N-[3-chloro-2-(ethoxycarbonyl)-4-fluoro-phenyl]-glycine ethyl ester in 15 ml of ether. The mixture was boiled under reflux for 1 hour and, after cooling, treated with water. The mixture was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction. 2.7 g (88.5%) of crude ethyl 4-chloro-5-fluoro-3-hydroxyindole-2-carboxylate were obtained. A

sample was recrystallized from methanol and then showed a m.p. of 191-192°.

c) A suspension of 2 g (7.7 mmol) of ethyl 4-chloro-5-fluoro-3-hydroxyindole-2-carboxylate in 70 ml of methanol was treated with 50 ml of a 60% ethereal diazomethane solution. 50 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off. The residue was recrystallized from methanol. There were obtained 1.25 g (59%) of ethyl 4-chloro-5-fluoro-3-methoxyindole-2-carboxylate as fine white crystals with m.p. 191-192°.

d) A solution of 1.2 g (4.4 mmol) of ethyl 4-chloro-5-fluoro-3-methoxyindole-2-carboxylate in 22 ml of dibromoethane was treated with 22 ml of 28% NaOH and 44 mg (0.14 mmol) of tetrabutylammonium bromide. The mixture was stirred at room temperature for 1.5 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 45 ml of liquid ammonia and stirred in an autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. There were obtained 1.1 g (97.3%) of 9-chloro-8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as beige crystals with m.p. 189-193°.

e) A solution of 1.1 g (4.1 mmol) of 9-chloro-8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 45 ml of dry THF was treated with 0.32 g (8.4 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water and 5 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 50 ml of ethanol and treated with 20 ml of saturated ethanolic HCl solution. There was obtained 0.55 g (63%) of 9-chloro-8-fluoro-

1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 243-245°.

Example 9

a) A solution of 1.7 g (10 mmol) of 4-methyl-isatoic anhydride in 20 ml of dimethyl sulphoxide was treated with 1 g of powdered KOH and with 1.83 g (11 mmol) of ethyl bromoacetate and stirred at room temperature for 3 hours. Then, 30 ml of ethanol were added to the mixture and it was stirred for half an hour. The mixture was extracted with ether and water. The organic phase was dried with sodium sulphate and the solvent was distilled off. The residue was distilled in a bulb-tube at a bath temperature of 180° and a pressure of 0.5 mm. There were obtained 1.6 g (60%) of N-[2-(ethoxycarbonyl)-3-methyl-phenyl]-glycine ethyl ester as a colourless oil.

b) A solution of 0.6 g (26 mmol) of sodium in 35 ml of ethanol was treated with a suspension of 5.3 g (20 mmol) of N-[2-(ethoxycarbonyl)-3-methyl-phenyl]-glycine ethyl ester in 35 ml of ether. The mixture was boiled under reflux for 1 hour and, after cooling, treated with water. The mixture was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction. 3.4 g (77.6%) of crude ethyl 3-hydroxy-4-methyl-indole-2-carboxylate were obtained. A sample was recrystallized from ethanol and then showed a m.p. of 124-125°.

c) A suspension of 2 g (9.1 mmol) of ethyl 3-hydroxy-4-methyl-indole-2-carboxylate in 20 ml of methanol was treated with 100 ml of a 60% ethereal diazomethane solution. 50 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off. The residue was recrystallized from ethanol. There were obtained 1.27 g (60%) of ethyl 3-methoxy-4-methyl-indole-2-carboxylate as white crystals with m.p. 109-110°.

d) A solution of 1 g (4.3 mmol) of ethyl 3-methoxy-4-methyl-indole-2-carboxylate in 20 ml of dibromoethane was treated with 20 ml of 28% NaOH and 44 mg (0.14 mmol) of tetrabutylammonium bromide. The mixture was stirred at 80° for 2 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 45 ml of liquid ammonia and stirred in an autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. There was obtained 0.9 g (91%) of 1,2,3,4-tetrahydro-10-methoxy-9-methyl-pyrazino[1,2-a]indol-1-one as beige crystals with m.p. 201-202°.

e) A solution of 0.83 g (3.6 mmol) of 1,2,3,4-tetrahydro-10-methoxy-9-methyl-pyrazino[1,2-a]indol-1-one in 45 ml of dry THF was treated with 0.28 g (7.5 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water and 5 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 40 ml of ethanol and treated with 20 ml of saturated ethanolic HCl solution. There was obtained 0.51 g (56%) of 1,2,3,4-tetrahydro-10-methoxy-9-methyl-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 231-233°.

Example 10

a) A suspension of 4.8 g (22 mmol) of methyl 6-trifluoromethylanthranilate and 2.5 g (23.3 mmol) of sodium carbonate in 20 ml (177.5 mmol) of ethyl bromoacetate was stirred at 80° for 20 hours. The mixture was evaporated in a vacuum and the residue was treated with 50 ml of water, 5 ml of ethanol and 5 ml of a 25% ammonia solution. The mixture was extracted with dichloromethane and the organic phase was dried with sodium sulphate. The solvent was distilled off and there were obtained 5.9 g (93%) of N-[3-trifluoromethyl-2-(methoxy-

carbonyl)-phenyl]-glycine methyl ester as an orange oil which was used in the next step without further purification.

b) A solution of 0.43 g (18.6 mmol) of sodium in 20 ml of methanol was treated with a suspension of 4.5 g (15.5 mmol) of N-[3-trifluoromethyl-2-(methoxycarbonyl)-phenyl]-glycine methyl ester in 100 ml of ether. The mixture was stirred at room temperature for 2 hours and treated with water. The aqueous phase was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction. 1.8 g (45%) of methyl 4-trifluoromethyl-3-hydroxyindole-2-carboxylate were obtained.

c) A solution of 1.8 g (6.9 mmol) of methyl 4-trifluoromethyl-3-hydroxyindole-2-carboxylate in 70 ml of methanol was treated with 100 ml of a 60% ethereal diazomethane solution. 50 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off. There were obtained 1.9 g (quant.) of ethyl 4-trifluoromethyl-3-methoxyindole-2-carboxylate which was used in the next step without further purification.

d) A solution of 1.9 g (6.9 mmol) of methyl 4-trifluoromethyl-3-methoxyindole-2-carboxylate in 35 ml of dibromoethane was treated with 35 ml of 28% NaOH and 100 mg (0.1 mmol) of tetrabutylammonium bromide. The mixture was stirred at 50° for 2 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 50 ml of liquid ammonia and stirred in an autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. 0.98 g (49.5%) of 9-trifluoromethyl-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one was obtained.

e) A solution of 0.68 g (2.4 mmol) of 9-trifluoromethyl-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 50 ml of dry THF was treated with 0.36 g (9.6 mmol) of lithium

aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water and 20 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 40 ml of ethanol and treated with 20 ml of saturated ethanolic HCl solution. There was obtained 0.6 g (56%) of 9-trifluoromethyl-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 244-245°.

Example 11

a) A suspension of 1.7 g (7.7 mmol) of methyl 3-methylthio-indole-2-carboxylate in 50 ml of dibromoethane was treated with 50 ml of 28% NaOH and 100 mg (0.3 mmol) of tetrabutylammonium bromide. The mixture was stirred at 50° for 2 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the residue was suspended in 50 ml of liquid ammonia and stirred in an autoclave at 80° for 24 hours. After evaporation of the ammonia the residue was extracted with water and ethyl acetate. The organic phase was dried and evaporated. The residue was recrystallized from ethyl acetate. There was obtained 0.73 g (40%) of 1,2,3,4-tetrahydro-10-methylthio-pyrazino[1,2-a]indol-1-one as white crystals with m.p. 148-156°.

b) A solution of 0.68 g (3 mmol) of 1,2,3,4-tetrahydro-10-methylthio-pyrazino[1,2-a]indol-1-one in 30 ml of dry THF was treated with 228 mg (6 mmol) of lithium aluminium hydride and boiled under reflux for two hours. The excess hydride was decomposed cautiously with water and 20 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 10 ml of ethanol and treated with 10 ml of saturated ethanolic HCl solution. There was obtained 0.52 g (70%) of 1,2,3,4-tetrahydro-10-methylthio-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 236-237° (dec.).

Example 12

a) A suspension of 5 g (22.7 mmol) of methyl 4,6-dichloroanthranilate and 2.4 g (22.6 mmol) of sodium carbonate in 20 ml (179 mmol) of ethyl bromoacetate was stirred at 80° for 40 hours. The mixture was evaporated in a vacuum and the residue was treated with 90 ml of water, 9 ml of ethanol and 9 ml of a 25% ammonia solution. The mixture was stirred for half an hour and extracted with 200 ml of ether. The organic phase was washed with water. After drying with sodium sulphate and removing the solvent there were obtained 7 g (96.3%) of N-[3,5-dichloro-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester as an orange oil which is used in the next step without further purification.

b) A solution of 0.6 g (26 mmol) of sodium in 20 ml of ethanol was treated with a suspension of 5. g (15.6 mmol) of N-[3,5-dichloro-2-(ethoxycarbonyl)-phenyl]-glycine ethyl ester in 10 ml of ether. The mixture was boiled under reflux for 1 hour and, after cooling, treated with water. The aqueous phase was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction. After recrystallization from ethanol there were obtained 2.2 g (51%) of ethyl 3-hydroxy-4,6-dichloro-indole-2-carboxylate as brownish crystals with m.p. 183-185°.

c) A suspension of 2 g (7.3 mmol) of ethyl 3-hydroxy-4,6-dichloro-indole-2-carboxylate in 30 ml of methanol was treated with 100 ml of a 60% ethereal diazomethane solution. The mixture was stirred at room temperature for half an hour. The solvent was distilled off. The residue was recrystallized from methanol. There were obtained 1.5 g (71%) of ethyl 3-methoxy-4,6-dichloro-indole-2-carboxylate as beige crystals with m.p. of 173-175°.

d) A solution of 1.5 g (5.2 mmol) of ethyl 3-methoxy-4,6-dichloro-indole-2-carboxylate in 30 ml of dibromoethane was treated with 30 ml of 28% NaOH and 100 mg (0.1 mmol) of tetrabutylammonium bromide. The mixture was stirred at 50° for

2 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 70 ml of liquid ammonia and stirred in an autoclave at 80° for 23 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. There was obtained 0.97 g (65.5%) of 7,9-dichloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as beige crystals with a m.p. of 228-232°.

e) A solution of 0.94 g (3.3 mmol) of 7,9-dichloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 25 ml of dry THF was treated with 300 mg (7.9 mmol) of lithium aluminium hydride and boiled under reflux for 2 hours. The excess hydride was decomposed cautiously with water, the mixture was diluted with 20 ml of THF and 9 g of sodium sulphate were added thereto. The mixture was filtered and concentrated. The residue was dissolved in 20 ml of ethanol. The salt was precipitated by the addition of 10 ml of saturated ethanolic HCl solution. There was obtained 0.65 g (73%) of 7,9-dichloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals which decomposed above 245°.

Example 13

a) A solution of 2.4 g (8.6 mmol) of N-[6-bromo-2-(carboxy)-phenyl]-glycine in 100 ml of methanol was treated with 150 ml of a 60% ethereal diazomethane solution. A further 50 ml of this diazomethane solution was added after 30 min. and the reaction solution was stirred for 15 min. The solution was evaporated and there were obtained 2.6 g (quant.) of N-[6-bromo-2-(methoxy-carbonyl)-phenyl]-glycine methyl ester as a pale brown oil which was used in the next step without further purification.

b) A solution of 0.25 g (10.6 mmol) of sodium in 12 ml of methanol was treated with a suspension of 2.6 g (8.8 mmol) of N-[6-bromo-2-(methoxycarbonyl)-phenyl]-glycine methyl ester in

12 ml of ether. The mixture was boiled under reflux for 1 hour and, after cooling, treated with water. The aqueous phase was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction. There were obtained 2 g (86%) of methyl 7-bromo-3-hydroxy-indole-2-carboxylate as beige crystals with m.p. 255-258°.

c) A suspension of 1.9 g (7. mmol) of methyl 7-bromo-3-hydroxy-indole-2-carboxylate in 120 ml of methanol was treated with 150 ml of a 60% ethereal diazomethane solution. The mixture was stirred at room temperature for half an hour. The solvent was distilled off. There were obtained 2 g (quant.) of methyl 7-bromo-3-methoxy-indole-2-carboxylate as a brown oil which is used in the next step without further purification.

d) A solution of 3.73 g (13.1 mmol) of methyl 7-bromo-3-hydroxy-indole-2-carboxylate in 65 ml of dibromoethane was treated with 65 ml of 28% NaOH and 100 mg (0.1 mmol) of tetrabutylammonium bromide. The mixture was stirred at 50° for 2 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 70 ml of liquid ammonia and stirred in an autoclave at 80° for 23 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. There was obtained 0.97 g (65.5%) of 6-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as beige crystals with a m.p. of 148-150°.

e) A solution of 0.9 g (3 mmol) of 6-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 60 ml of dry THF was treated with 60 ml of a 1N diborane solution in THF and boiled under reflux for two hours. The excess hydride was decomposed with 5 ml of saturated ethanolic HCl and the mixture was heated under reflux for one hour. The mixture was made basic with concentrated sodium hydroxide solution and extracted with ethyl acetate and water. The organic phase was dried with

sodium sulphate and the solvent was removed. The residue was dissolved in 30 ml of ethanol and by the addition of 10 ml of saturated ethanolic HCl solution at 0° there was obtained 0.5 g (51.6%) of 6-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 226°.

Example 14

a) A suspension of 2 g (9.3 mmol) of ethyl 4-chloro-5-fluoroanthranilate and 1 g (9.3 mmol) of sodium carbonate in 8 ml (71 mmol) of ethyl bromoacetate was stirred at 80° for 30 hours. The mixture was evaporated in a vacuum and the residue was treated with 33 ml of water, 3.3 ml of ethanol and 3.3 ml of 25% ammonia solution. The mixture was extracted with ethyl acetate and the organic phase was dried with sodium sulphate. The solvent was distilled off and there were obtained 2.75 g (98.5%) of N-[5-chloro-2-(ethoxycarbonyl)-4-fluoro-phenyl]-glycine ethyl ester as an orange oil which was used in the next step without further purification.

b) A solution of 0.25 g (10.9 mmol) of sodium in 11.5 ml of ethanol was treated with a suspension of 2.75 g (9 mmol) of N-[5-chloro-2-(ethoxycarbonyl)-4-fluoro-phenyl]-glycine ethyl ester in 15 ml of ether. The mixture was boiled under reflux for 2 hours and, after cooling, treated with water. The mixture was adjusted to pH 8 with dry ice and the separated crystals were filtered off under suction. There were obtained 2.0 g (85.8%) of ethyl 6-chloro-5-fluoro-3-hydroxyindole-2-carboxylate as brown crystals with a m.p. of 186-187° (dec.).

c) A suspension of 2 g (7.7 mmol) of ethyl 6-chloro-5-fluoro-3-hydroxyindole-2-carboxylate in 70 ml of methanol was treated with 50 ml of a 60% ethereal diazomethane solution. 30 ml of this solution were again added after half an hour and the mixture was stirred at room temperature for a further half an hour. The solvent was distilled off. The residue was recrystallized from methanol. There were obtained 1.34 g (63.6%) of ethyl 6-chloro-

5-fluoro-3-methoxyindole-2-carboxylate as white crystals with m.p. 184-185°.

d) A solution of 1.33 g (4.9 mmol) of ethyl 6-chloro-5-fluoro-3-methoxyindole-2-carboxylate in 24 ml of dibromoethane was treated with 24 ml of 28% NaOH and 50 mg (0.15 mmol) of tetrabutylammonium bromide. The mixture was stirred at 40° for 1.5 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was evaporated and there were obtained 1.85 g (quant.) of ethyl 1-(2-bromoethyl)-6-chloro-5-fluoro-3-methoxyindole-2-carboxylate as yellow crystals with m.p. 81.5-82.5°.

e) A suspension of 1.8 g (4.7 mmol) of ethyl 1-(2-bromoethyl)-6-chloro-5-fluoro-3-methoxyindole-2-carboxylate in 50 ml of liquid ammonia was stirred in autoclave at 80° for 18 hours. After evaporation of the ammonia the residue was taken up in water, triturated and filtered off under suction. There were obtained 1.22 g (96%) of 7-chloro-8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one as beige crystals with m.p. 211-212°.

f) A solution of 1.2 g (4.4 mmol) of 7-chloro-8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indol-1-one in 50 ml of dry THF was treated with 0.35 g (9.2 mmol) of lithium aluminium hydride and boiled under reflux for 1.5 hours. The excess hydride was decomposed cautiously with water and 6 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 50 ml of ethanol and treated with 20 ml of saturated ethanolic HCl solution. There was obtained 0.75 g (58%) of 7-chloro-8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole hydrochloride as white crystals with m.p. 224° (dec.).

Example 15

a) A solution of 0.48 g of ethyl 4-chloro-5-fluoro-indole-2-carboxylate in 10 ml of dibromoethane was treated with 10 ml of 28% NaOH and 20 mg (0.06 mmol) of tetrabutylammonium bromide. The mixture was stirred at 50° for 2 hours. The phases were separated and the aqueous phase was extracted with toluene. The combined organic phases were washed with water and dried over sodium sulphate. The solvent was distilled off and the solid residue was suspended in 20 ml of liquid ammonia and stirred in an autoclave at 80° for 23 hours. After evaporation of the ammonia the residue was taken up in water, stirred and filtered off under suction. There was obtained 0.43 g (90%) of 9-chloro-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-one as beige crystals with a m.p. of 248-250°.

b) A solution of 0.42 g (1.7 mmol) of 9-chloro-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-one in 20 ml of dry THF was treated with 150 mg (4 mmol) of lithium aluminium hydride and boiled under reflux for 2 hours. The excess hydride was cautiously decomposed with water and 2 g of sodium sulphate were added to the mixture. After filtration and concentration of the filtrate the residue was dissolved in 20 ml of ethanol and treated with saturated ethanolic HCl solution. There was obtained 0.2 g (43%) of 9-chloro-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride as white crystals which decomposed above 268°.

Example A

Tablets of the following composition are manufactured in a conventional manner:

	mg/tablet
Active ingredient	100
Powd. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are manufactured in the usual manner:

	mg/tablet
Active ingredient	200
Powd. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

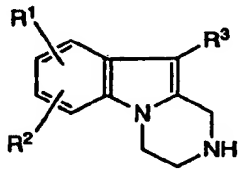
Capsules of the following composition are manufactured:

	mg/capsule
Active ingredient	50
Cryst. lactose	60
Microcristalline cellulose	34
Talc	5
Magnesium stearate	1
capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The finished mixture is filled into hard gelatine capsules of suitable size.

Claims 2097465

1. Compounds of the general formula



I

wherein R^1 signifies hydrogen, halogen, trifluoromethyl, lower alkyl, hydroxy or lower alkoxy, R^2 signifies hydrogen or halogen and R^3 signifies hydrogen, lower alkoxy or lower alkylthio, with the proviso that R^3 can only signify hydrogen when R^1 and R^2 are both different from hydrogen,
and pharmaceutically acceptable acid addition salts of the compounds of formula I.

2. Compounds according to claim 1, wherein R^3 is different from hydrogen.

3. Compounds according to claim 2, wherein R^3 signifies lower alkoxy.

4. Compounds according to any one of claims 1 or 3, wherein R^1 signifies hydrogen or halogen and R^2 signifies halogen.

5. Compounds according to claim 1, wherein R^3 singifies hydrogen and R^1 and R^2 each signify halogen.

6. 9-Chloro-8-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole.

7. 8-Fluoro-10-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]indole.

8. 9-Fluoro-10-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]indole.

9. 9-Bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole.

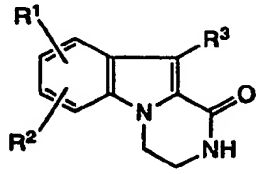
10. 9-Chloro-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole.

11. 8-Chloro-10-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]indole;

7-chloro-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole; and

8-bromo-1,2,3,4-tetrahydro-10-methoxy-pyrazino-[1,2-a]indole.

12. Compounds of the general formula



II

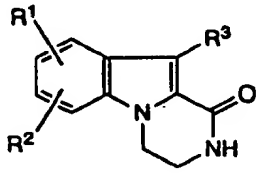
wherein R^1, R^2 and R^3 have the significance given in claim 1.

13. Compounds according to any one of claims 1-11 as well as pharmaceutically acceptable acid addition salts thereof for use as therapeutically active substances.

14. Compounds according to any one of claims 1-11 as well as pharmaceutically acceptable acid addition salts thereof for use as therapeutically active substances for the treatment or prophylaxis of central nervous disorders such as depression, bipolar disorders, anxiety, sleep and sexual disorders, psychosis, schizophrenia, migraine and other conditions associated with cephalic pain or other pain types, personality disorders and obsessive-compulsive disorders, social phobia or panic disorders, mental organic disorders, mental disorders in childhood, aggressiveness, age-associated memory impairement and behavioral symptoms, addiction, obesity, bulimia etc.; neural

damage resulting from trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of gastrointestinal tract motility.

15. A process for the manufacture of compounds according to any one of claims 1-11 and of pharmaceutically acceptable acid addition salts thereof, which process comprises reducing a compound of the general formula



II

wherein R^1, R^2 and R^3 have the significance given in claim 1,

and, if desired, converting a compound of formula I obtained into a pharmaceutically acceptable acid addition salt.

16. A medicament containing a compound according to any one of claims 1-11 and a therapeutically inert carrier material.

17. A medicament according to claim 16 for the treatment or prophylaxis of central nervous disorders such as depression, bipolar disorders, anxiety, sleep and sexual disorders, psychosis, schizophrenia, migraine and other conditions associated with cephalic pain or other pain types, personality disorders and obsessive-compulsive disorders, social phobia or panic disorders, mental organic disorders, mental disorders in childhood, aggressiveness, age-associated memory impairement and behavioral symptoms, addiction, obesity, bulimia etc.; neural damage resulting from trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of gastrointestinal tract motility.

18. The use of compounds according to any one of claims 1-11 in the treatment or prophylaxis of illnesses.

19. The use of compounds according to any one of claims 1-11 in the treatment or prophylaxis of central nervous disorders such as depression, bipolar disorders, anxiety, sleep and sexual disorders, psychosis, schizophrenia, migraine and other conditions associated with cephalic pain or other pain types, personality disorders and obsessive-compulsive disorders, social phobia or panic disorders, mental organic disorders, mental disorders in childhood, aggressiveness, age-associated memory impairement and behavioral symptoms, addiction, obesity, bulimia etc.; neural damage resulting from trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of gastrointestinal tract motility; or for the manufacture of corresponding medicaments.

20. Compounds according to any one of claims 1-11, whenever prepared by the process of claim 15 or by an obvious chemical equivalent thereof.

21. The invention as herein described.

22. A method for the treatment or prophylaxis of central nervous disorders such as depression, bipolar disorders, anxiety, sleep and sexual disorders, psychosis, schizophrenia, migraine and other conditions associated with cephalic pain or other pain types, personality disorders and obsessive-compulsive disorders, social phobia or panic disorders, mental organic disorders, mental disorders in childhood, aggressiveness, age-associated memory impairement and behavioral symptoms, addiction, obesity, bulimia etc.; neural damage resulting from trauma, stroke, neurodegenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal

disorders such as dysfunction of gastrointestinal tract motility; which comprises administering to a host in need of such treatment or prophylaxis an effective amount of a compound according to any one of claims 1-11.

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